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(54) Title: LOW-CONCENTRATION CAPSAICIN PATCH AND METHODS FOR TREATING NEUROPATHIC PAIN

(57) Abstract: Described here are patches and methods for treating neuropathic pain. In some variations, the neuropathic pain-relieving patch comprises capsaicin or a capsaicin analog, wherein the concentration of the capsaicin or capsaicin analog is less than 1% by weight, and a penetration enhancer, wherein the patch is capable of relieving neuropathic pain over a sustained period of time. The penetration enhancer may be any suitable penetration enhancer. The patches may also include oils, viscosity increasing agents, and the like. In some variations, the pain-relieving patches comprise capsaicin, or an, wherein the concentration of the capsaicin or analog is less than 1%, and a penetration enhancer, whereby delivery of capsaicin from the patch continues for at least an hour, and whereby a single use of the patch provides a therapeutic benefit for at least one month, two months, or three months. Methods for treating neuropathic pain are also described.



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LOW-CONCENTRATION CAPSAICIN PATCH AND METHODS FOR TREATING NEUROPATHIC PAIN

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Serial No. 60/666,880, filed March 30, 2005, which is hereby incorporated by reference in its entirety.

FIELD

[0002] The patches and methods described here are in the field of dermal drug delivery, and specifically, dermal delivery of capsaicin or a capsaicin analog for the treatment of neuropathic pain.

BACKGROUND

[0003] Almost four million people in the United States are afflicted with neuropathic pain syndromes (Bennett GJ. Neuropathic pain: new insights, new interventions. *Hosp Pract.* 1998 Oct. 15; 33(10):95-8), and the prevalence is rising (Dworkin RH. An Overview of Neuropathic Pain: Syndromes, Symptoms, Signs, and Several mechanisms. *Clin J Pain.* 2002 Nov-Dec; 18(6):343-9). Neuropathic pain may last many years and can even be permanent. Due to poor efficacy of existing medicines, neuropathic pain has a devastating impact on patients' quality of life and high societal costs (Harden N, Cohen M. Unmet Needs in the Management of Neuropathic Pain. *J Pain Symptom Management.* 2003. 25(5 Suppl):S12-S17). Causes of neuropathic pain are highly diverse and include reactivation of latent viruses, direct trauma to nerves, diabetes, and HIV-infection and therapy (*id.*).

[0004] Currently approved treatments for post-herpetic neuralgia (PHN) are oral gabapentin (Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the Treatment of Postherpetic Neuralgia: a Randomized Controlled Trial. *JAMA.* 1998 Dec 2; 280(21):1837-42; Rice AS, Maton S; Postherpetic Neuralgia Study Group. Gabapentin in Postherpetic Neuralgia: A Randomised, Double Blind, Placebo Controlled Study. *Pain.* 2001. 94:215-24) and the topical lidocaine patch (Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine Patch: Double-Blind Controlled Study of a New Treatment Method for Post-Herpetic Neuralgia. *Pain.* 1996. 65:39-44; Galer BS, Jensen MP, Ma T, Davies PS, Rowbotham MC. The Lidocaine Patch 5% Effectively Treats All Neuropathic Pain Qualities: Results of a

Randomized, Double-Blind, Vehicle-Controlled, 3-week Efficacy Study with use of the Neuropathic Pain Scale. *Clin J Pain*. 2002 Sep-Oct; 18(5):297-301). Both have shown efficacy, but they only led to partial pain relief in a subset of patients. Gabapentin appears to be better tolerated than other anticonvulsants, but CNS-related side effects such as somnolence and dizziness, as well as the need for dose-titration and three times daily dosing, frequently limit its use in some patients (Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine Patch: Double-Blind Controlled Study of a New Treatment Method for Post-Herpetic Neuralgia. *Pain*. 1996 Apr; 65(1):39-44). There are no FDA-approved pain medicines specifically for painful HIV-associated neuropathy. Speaking generally in the field of neuropathic pain management, even with the recent approvals of Lyrica® (pregabalin) and Cymbalta® (duloxetine), there remains a significant medical need for a therapeutic modality with substantial efficacy and a favorable side effect profile.

[0005] Capsaicin, the pungent ingredient in chili peppers, activates vanilloid receptors (TRPV1) expressed in cutaneous nociceptive sensory nerve fibers, leading acutely to burning pain sensations followed by prolonged functional inactivation of these nociceptors (Caterina MJ, Julius D. The Vanilloid Receptor: a Molecular Gateway to the Pain Pathway. *Annu. Rev. Neurosci*. 2001. 24:487-517). Topical low-concentration capsaicin creams have shown efficacy in PHN in controlled clinical trials, but their practical use has been hampered by the inconvenience of multiple daily applications needed to produce efficacy. Moreover, each cream application is often associated with painful burning sensations (Hautkappe M, Roizen MF, Toledaon A, Roth S, Jeffries JA, Ostermeier AM. Review of the Effectiveness of Capsaicin for Painful Cutaneous Disorders and Neural Dysfunction. *Clin. J. Pain*. 1998. 14:97-106).

[0006] In uncontrolled compassionate use in various neuropathic pain syndromes, one-time applications of high-concentration capsaicin creams (e.g., 5 - 10% w/w) have shown promising pain relief (Robbins WR, Staats PS, Levine J, et al. Treatment of Intractable Pain with Topical Large-Dose Capsaicin: Preliminary Report. *Anesth. Analg*. 1998. 86:579-583). Patches with a high concentration (e.g., 8% w/w) of capsaicin have also undergone clinical evaluation (See: D Simpson, S Brown, S Chang, J Jermano and C107 Study Group. Controlled Study of High-Concentration Capsaicin Patch for Painful HIV-Associated Distal Sensory Polyneuropathy. 2006. 13th Conference on Retroviruses and Opportunistic Infections). Unfortunately, the high-concentration capsaicin creams described above displayed very high levels of pungency, often requiring patients to undergo regional nerve blocks in order to tolerate

the treatment procedure (Robbins et al., 1998). High-concentration capsaicin patches display lower levels of pungency, but still induce a substantial percentage of patients to ask for opioid analgesics during and/or following treatment procedures.

[0007] Accordingly, it would be desirable to have low-concentration capsaicin patches for the treatment of neuropathic pain, as they may be better tolerated than high-concentration patches and high-concentration capsaicin creams.

SUMMARY

[0008] Described herein are patches and methods for treating neuropathic pain. In general, the neuropathic pain-relieving patches include capsaicin or a capsaicin analog at a concentration of less than about 1% by weight and a penetration enhancer. The patches are typically formulated to relieve pain for a sustained time period, for example, at least about one week, at least about two weeks, at least about one month, at least about two months, or at least about three months or more.

[0009] Penetration enhancers suitable for use in the neuropathic pain-relieving patches include, but are not limited to, ethers, esters, alcohols, fatty acids, terpenes, amines, and mixtures thereof. In particular, penetration enhancers that may be used include *l*-menathone, dimethyl isosorbide, caprylic alcohol, lauryl alcohol, oleyl alcohol, ethylene glycol, diethylene glycol monoethyl ether, triethylene glycol, butylene glycol, valeric acid, pelargonic acid, caproic acid, caprylic acid, lauric acid, oleic acid, isovaleric acid, isopropyl butyrate, isopropyl hexanoate, butyl acetate, methyl acetate, methyl valerate, ethyl oleate, poloxamer, *d*-piperitone, methylnonenoic acid, methylnonenoic alcohol, and *d*-pulegone, and mixtures thereof.

[0010] The pain-relieving patches typically include a self-adhesive matrix, but any polymeric matrix may be employed, so long as the patch is capable of delivering capsaicin or a capsaicin analog and relieving neuropathic pain over the desired time period. In one variation, the self-adhesive matrix includes an amine-resistant polysiloxane. In this particular variation, it may be desirable to incorporate a silicone oil to the matrix. In another variation, the self-adhesive matrix includes polyisobutylene adhesives in combination with plasticizer which is mineral oil. In yet another variation, adhesive can be acrylate-based whereby co-polymers of alkyl acrylates with acrylamide or acetonitrile. Such polymers can range from C₄ to C₈.

[0011] Also described here are methods for treating neuropathic pain. The general method includes applying a neuropathic pain-relieving patch that has less than about 1% capsaicin or a capsaicin analog for a period of about 30 minutes, a period of about 60 minutes, but not longer than a period of about 120 minutes.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIG. 1 is a flow diagram showing an exemplary process for manufacturing the patches described herein.

[0013] FIG. 2 is a graph showing pooled data from all patients in Studies 1, 2 and 3 receiving low-concentration capsaicin patch treatments. Studies 1 and 2 enrolled subjects with PHN. Study 3 enrolled subjects with HIV-AN.

DETAILED DESCRIPTION

[0014] The patches and methods described here treat neuropathic pain by dermally delivering an active agent, i.e., capsaicin or a capsaicin analog. As used herein, the term “dermally” or “dermal” refers to topical delivery of drug mainly to the skin layers with no drug or minimal drug reaching the systemic circulation. The patches generally include a self-adhesive matrix and a backing layer, and less than about 1% by weight capsaicin or a capsaicin analog and a penetration enhancer in the self-adhesive matrix. Clinical data has been generated from patches containing 0.04% w/w capsaicin, and is provided below.

[0015] The primary advantage of the low-concentration patch is that tolerability is improved due to reduced pungency. That is, patients exposed to the low-concentration patch will be less likely to ask to have the patch removed during a treatment procedure. They will also likely consume lower amounts of opioid pain relievers in order to deal with treatment-associated pain. As with all topical capsaicin-based pain reducing products, the theory is that hyperactive nociceptors in the skin are pathologically active in patients with peripheral neuropathic pain syndromes. Exposure to capsaicin causes these pathologically hyperactive nerve fibers to cease functioning for an extended period of time; this process is often referred to as ‘desensitization’ (Bley, K.R. Recent developments in transient receptor potential vanilloid receptor 1 agonist-based therapies. *Expert Opin Investig Drugs*. 2004. 13:1445-56). Although the low-concentration patch may not provide a degree of average pain relief as great as a high-

concentration capsaicin patch, for a subset of patients, the low-concentration patch induces persistent and clinically significant pain reductions without significant side effects.

[0016] Active agents. Active agents that may be used in the low-concentration patches include capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, homodihydrocapsaicin, nonivamide, *cis*-capsaicin, olvanil, arvanil and analogs of capsaicin such as capsaicin esters and derivatives of the amide side chain.

[0017] Penetration enhancers. The penetration enhancers for use in the neuropathic pain-relieving patches may be any suitable penetration enhancer. For example, the penetration enhancer may be an ether, ester, alcohol, fatty acid, terpene, amine, or a mixture thereof. Specific penetration enhancers suitable for use with the patches described here include those selected from the group consisting of *l*-menathone, dimethyl isosorbide, caprylic alcohol, lauryl alcohol, oleyl alcohol, ethylene glycol, diethylene glycol monoethyl ether, triethylene glycol, butylene glycol, valeric acid, pelargonic acid, caproic acid, caprylic acid, lauric acid, oleic acid, isovaleric acid, isopropyl butyrate, isopropyl hexanoate, butyl acetate, methyl acetate, methyl valerate, ethyl oleate, poloxamer, *d*-piperitone, methylnonenoic acid, methylnonenoic alcohol, and *d*-pulegone, and mixtures thereof. In one variation, the penetration enhancer is diethylene glycol monoethyl ether.

[0018] Matrix materials. The pain-relieving patch may comprise a self-adhesive matrix, for example, an amine-resistant polysiloxane. In one variation, the amine resistant polysiloxane comprises a mixture of medium and high tack polysiloxane. A silicone oil may be added to the polysiloxane adhesive or mixture thereof. Silicone oil enhances adhesive properties and may constitute from 0.5 to 5% by weight of silicone oil. In another variation, the matrix comprises polyisobutylene adhesives in combination with plasticizer which is mineral oil. In yet another variation, the adhesive can be acrylate-based whereby co-polymers of alkyl acrylates with acrylamide or acetonitrile. Such polymers can range from C₄ to C₈.

[0019] Other additives. The neuropathic pain-relieving patch may also comprise a silicone oil, a viscosity increasing agent, a penetration enhancer or a combination thereof. The viscosity increasing agent may be, for example, ethylcellulose, hydropropylcellulose, or mixtures thereof. The penetration enhancer may be, as example, fatty acids (linear or branched), fatty acid esters, organic acids, ethers, amides, amines, hydrocarbons, alcohols, phenols, polyols,

fatty alcohols, surfactants (anionic, cationic, nonionic or bile salts), ureas, terpenes (hydrocarbons, alcohols, ketones, oils, oxides).

[0020] Backing layer. The backing layer typically is made from a polyester film and generally about 10 to about 20 μm thick. The backing layer may also be made from such materials as ethylene vinyl acetate, polyethylene, polyurethane, pigmented polyethylene plus polyester with/without aluminum vapor coating.

[0021] In one variation, the pain-relieving patches include 0.04% by weight or less of capsaicin or a capsaicin analog, 10-20% by weight of diethylene glycol monoethyl ether, 0-2% by weight of ethylcellulose, 0-5% by weight of silicone oil, and 58-85% by weight of a self-adhesive polysiloxane. These patches may also comprise a backing layer, for example, the polyester films mentioned above.

[0022] In another variation, the pain-relieving patches comprise capsaicin, or a capsaicin analog, wherein the concentration of the capsaicin or capsaicin analog is less than 1%, and a penetration enhancer, whereby delivery of capsaicin from the patch continues for at least an hour, and whereby a single use of the patch provides a therapeutic benefit for at least one month, two months, or three months. These patches may further include those penetration enhancers mentioned above. In some variations, the penetration enhancer is diethylene glycol monoethyl ether. The patches may also comprise a self-adhesive matrix (such as an amine-resistant polysiloxane), a silicone oil, a viscosity increasing agent, and/or a backing layer. In some variations, the viscosity increasing agent is ethylcellulose.

[0023] Methods for treating neuropathic pain are also described here. In general, the methods comprise the step of dermally delivering a single administration of capsaicin or a capsaicin analog by topically applying a low-concentration neuropathic pain-relieving patch to any area of the skin affected by neuropathic pain. The patch includes capsaicin or a capsaicin analog at a concentration of less than 1%. In some variations, the step of dermal delivery of the capsaicin or capsaicin analog provides a therapeutic benefit, i.e., significant relief of neuropathic pain, for at least one month, at least two months, or at least three months.

[0024] The clinical efficacy observed following single treatments of neuropathic pain patients with low-concentration patches is quite surprising given the requirement of repeated applications or chronic exposure for other low-concentration topical capsaicin products. For

instance, it is widely accepted that low-concentration creams (0.025 to 0.1% w/w) must be applied multiple times per day for efficacy to occur. Moreover, efficacy slowly develops over a period of weeks. According to the product label for Zostrix[®], a widely used over-the-counter capsaicin-containing cream: "Capsaicin must be used regularly every day as directed if it is to work properly. Even then, it may not relieve your pain right away. The length of time it takes to work depends on the type of pain you have. In persons with arthritis, pain relief usually begins within 1 to 2 weeks. In most persons with neuralgia, relief usually begins within 2 to 4 weeks, although with head and neck neuralgias, relief may take as long as 4 to 6 weeks. Once capsaicin has begun to relieve pain, you must continue to use it regularly 3 or 4 times a day to keep the pain from returning" (source: <http://www.drugs.com/cons/Zostrix.html>).

[0025] Similarly topical capsaicin-containing patches are also used to treat chronic lower back pain. Several clinical studies with a marketed capsaicin patch (37.4 μg capsaicin per cm^2 ; ABC Lokale Schmerz-Therapie Waerme-Pflaster[®]) have indicated that pain relief occurs gradually and that the patches must be worn every day. Keitel W, Frerick H, Kuhn U, Schmidt U, Kuhlmann M, Bredehorst A. Capsicum pain plaster in chronic non-specific low back pain. *Arzneimittelforschung*. 2001. 51(11):896-903. Frerick H, Keitel W, Kuhn U, Schmidt S, Bredehorst A, Kuhlmann M. Topical treatment of chronic low back pain with a capsicum plaster. *Pain*. 2003. 106(1-2):59-64.

Patches

[0026] The characteristics of the patches used in the methods of the present invention are described in Table 1.

Table 1: Characteristics of the Low-Concentration Capsaicin Patch

Material	Grade	Function	Weight (mg)
Drug Matrix			
<i>trans</i> -Capsaicin	cGMP Manufactured	Active Ingredient	179.0
Diethylene Glycol Monoethyl Ether (e.g., Transcutol [®])	USP26/NF21 DMF 5718	Solubilizer	430.0
Silicone Adhesive (amine resistant, BIO-PSA 4301)	DMF 7114	Adhesive	470.0

Silicone Adhesive (amine resistant, BIO-PSA 4201)	DMF 7114	Adhesive	1098.0
Silicone Oil, 12,500 cSt	USP26/NF21 for Dimethicone	Plasticizer	45.0
Formulation Aids (Removed During Drying)			
n-Heptane	Merck extra pure	Solvent for Adhesive	NA
Ethyl Cellulose N 50	USP26/NF21	Thickener	17.9
Backing Layer			
Polyethylene Terephthalate (PET) Film (matte, inner side siliconized) e.g. Hostphan MN 19 Thickness: 19 μ m	DMF 7373 21 CFR 177.1630	Backing Layer	694.4 - 887.6
Removable Protective Layer (Release Liner)			
Polyester film, fluoropolymer-coated. E.g., Scotchpak 1022 Thickness: 76.2 μ m	DMF 2610-E	Protective	1988.0 - 3220.0

[0027] Capsaicin is dissolved in a mixture of solubilizer and thickener. The adhesives and silicone oil are then added with a solvent. This mixture is dispersed, and the homogenized adhesive mass is coated onto a removable protective film liner. After removal of the solvent and drying, the matrix film is then laminated onto a backing layer. The laminate is wound into rolls and patches are punched out to the appropriate sizes before being packaged in heat-sealed Barex[®] pouches.

[0028] A self-explanatory flow diagram of the manufacturing process is shown in Figure 1.

Method of Use

[0029] The low-concentration capsaicin patches should be applied to the skin of a patient for about one (1) hour. However, this time may be lengthened or shortened depending on the particular patient's needs (e.g., based on the amount and/or severity of pain). Prior to application of the patch, a local anesthetic (e.g., in the form of a topically applied cream or a nerve block) is used to numb the skin of the treatment area. Applying the anesthetic helps ameliorate the sometimes intense burning sensations produced by the application of capsaicin to the skin. The painful area to be treated is defined by a health care provider, and patches are cut to provide complete coverage of the area. Following the approximate one-hour application, patch

pieces are removed and residual capsaicin from the treated area is removed with a cleansing gel. Capsaicin patches would be determined to have provided a therapeutic benefit if the pain symptoms reported by the patient prior to treatment were reduced following the treatment procedure.

EXAMPLES

[0030] The following examples are for illustrative purposes only and not intended to limit the scope of the invention as described herein and recited by the appended claims. For all three studies described in the following examples, the diagnoses of either postherpetic neuralgia ("PHN") or painful HIV-associated neuropathy (HIV-AN) was confirmed by medical history and physical examination. Patients who met the inclusion/exclusion criteria then completed a pain intensity diary for at least five days. Those continuing to meet eligibility criteria were randomized and treated.

[0031] The treatment procedure in all three studies began with application of a 4% w/w lidocaine-based topical cream to the skin treatment area for one hour. Subsequently, the anesthetic cream was removed and patches which had been cut to fit the treatment area were applied for one hour. After patch removal, a cleansing gel was applied for one minute and then wiped off. In case of significant pain during or immediately following patch application, an oral oxycodone elixir was available. In the PHN clinical studies, subjects were given 30 tablets of hydrocodone/acetaminophen (5 mg/500 mg) to be taken as needed for any procedure-related pain during the first five days after treatment. Patients were monitored for approximately three hours after patch removal and released. They were seen again at follow-up visits.

EXAMPLE 1 - STUDY 1

[0032] Because of its chronic and stable time course, and its occurrence in otherwise healthy and active individuals, postherpetic neuralgia (PHN) is a preferred clinical model of neuropathic pain for the initial study of new therapeutic modalities.

Study Population

[0033] A total of 299 patients with PHN that persisted at least 6 months after crusting of vesicles, without significant pain of other origin, were enrolled. The area of worst pain was less than 1000 cm² and did not include the face. Average pain intensity, rated by the patient twice daily on an 11-point scale (0 = no pain, 10 = worst pain imaginable), was between 3 and 8 during the screening period. Concomitant use of non-topical chronic pain medication was permitted, as long as the regimen remained stable for 3 weeks before treatment and throughout the study.

Study Design

[0034] Patients were randomized in a 3:3:3:1:1:1 ratio to receive either high-concentration (640 µg/cm² capsaicin) patches for durations of 30, 60 or 90 minutes or low-concentration (3.2 µg/cm² capsaicin) patches for 30, 60 or 90 minutes. The high-concentration and low-concentration patches were of identical appearance. Patients, investigators and sponsor staff were blinded to the treatment received until all data collection activities were completed. Because of prior reports that single applications of low-concentration capsaicin applications do not cause reductions in neuropathic pain, these low-concentration patches were deemed unlikely to exert a significant therapeutic effect.

EXAMPLE 2 - STUDY 2

Study Population

[0035] A total of 155 patients with PHN that persisted at least 3 months after crusting of vesicles, without significant pain of other origin, were enrolled. The area of worst pain was less than 1000 cm² and did not include the face. Average pain intensity, rated by the patient twice daily on an 11-point scale (0 = no pain, 10 = worst pain imaginable), was between 3 and 8 during the screening period. Concomitant use of non-topical chronic pain medication was permitted, as long as the regimen remained stable for 3 weeks before treatment and throughout the study.

Study Design

[0036] PHN patients were randomized in a 2:1 ratio to receive either high-concentration (640 $\mu\text{g}/\text{cm}^2$ capsaicin) or low-concentration (3.2 $\mu\text{g}/\text{cm}^2$ capsaicin) patches for 60 minutes. The high-concentration and low-concentration patches were of identical appearance. Patients, investigators and sponsor staff were blinded to the treatment received until all data collection activities were completed. Because of prior reports that low concentration capsaicin applications did not cause a sustained reduction in neuropathic pain, these low-concentration patches were deemed unlikely to exert a significant therapeutic effect.

EXAMPLE 3 - STUDY 3

Study Design

[0037] This double-blind, multi-center study randomized 307 subjects with HIV-AN symptoms ≥ 2 months, stratified by neurotoxic antiretroviral HIV treatment status, to single treatments with either high or low-concentration capsaicin patches for 90, 60 or 30 minutes. Patients were randomized in a 3:3:3:1:1:1 ratio to receive either high-concentration (640 $\mu\text{g}/\text{cm}^2$ capsaicin) patches for durations of 30, 60 or 90 minutes or low-concentration (3.2 $\mu\text{g}/\text{cm}^2$ capsaicin) patches for 30, 60 or 90 minutes. The high-concentration and low-concentration patches were of identical appearance. Patients, investigators and sponsor staff were blinded to the treatment received until all data collection activities were completed. Because of prior reports that single applications of low-concentration capsaicin applications do not cause reductions in neuropathic pain, these low-concentration patches were deemed unlikely to exert a significant therapeutic effect. Patches were applied to painful feet areas after a 60-minute topical anesthetic application. Subjects recorded daily pain intensity on an 11-point numeric pain rating scale (0 = no pain, 10 = worst possible pain). The primary efficacy endpoint was the percent change from baseline in mean "average pain for past 24 hours" scores for weeks 2 to 12.

Assessments

[0038] Efficacy in all three studies was assessed using patient-rated pain intensity scores (11-point scale) which were recorded twice daily in take-home diaries during the screening period and the entire 12-week study periods. Each evening, subjects rated their average pain over the preceding 24 hours. The primary efficacy endpoint was the change in the average of morning

and evening pain intensity from the baseline period to the follow-up period (average of weeks 2 to 8).

Patient Demographics

[0039] The study population for all three studies represented a wide range of patients with either PHN or HIV-AN. The baseline characteristics of the subjects to which the low-concentration patches were applied in the three studies are shown in Tables 2 - 4.

Table 2: Baseline Characteristics of Patients in Study 1

Number of Subjects with Low-Concentration Patch Applications	77
Age [years]	
Mean \pm SD	71.1 \pm 10.4
Range	27 - 91
Gender	
Female	39 (51%)
Male	38 (49%)
Ethnic Origin	
Caucasian	68 (88%)
African-American	1 (1%)
Other	7 (9%)
Duration of PHN [years]	
Mean \pm SD	3.8 \pm 4.5
Range	0.3 - 21.8
Baseline Pain Level	
Mean \pm SD	5.3 \pm 1.4
Range	2.5 - 8.1
Treatment Area Size [cm ²]	
Mean \pm SD	329 \pm 204
Range	32 - 893
Concomitant Medications	
Anticonvulsants	19 (25%)
Antidepressants	10 (13%)
Opioids	14 (18%)

SD = standard deviation.

Table 3: Baseline Characteristics of Patients in Study 2

Number of Subjects with 60-Minute Patch Applications	53
Age [years]	
Mean \pm SD	71.2 \pm 11.26
Range	35, 91
Gender	
Female	28 (53%)
Male	25 (47%)
Ethnic Origin	
Caucasian	45 (85%)
African-American	3 (6%)
Other	3 (6%)
Duration of Pain [years]	
Mean \pm SD	3.4 \pm 4
Range	0.3, 19.7
Baseline Pain Level [Average Pain in 24 Hours]	
Mean \pm SD	5.3 \pm 1.53
Range	2.5, 8.8
Treatment Area Size [cm ²]	
Mean \pm SD	348 \pm 216
Range	75, 963
Concomitant Medications	
Anticonvulsants	18 (34%)
Antidepressants	6 (11%)
Opioids	13 (25%)

Table 4: Baseline Characteristics of Patients in Study 3

Number of Patients with Low-Concentration Patch Applications	82
Age [years]	
Mean \pm SD	48.4 \pm 7.6
Range	33 - 70
Gender	
Female	3 (4%)
Male	79 (96%)
Race	
Caucasian	50 (61%)
African-American	18 (22%)
Other	14 (17%)
Duration of HIV-AN [years]	
Mean \pm SD	5.1 \pm 3.4
Range	0.1 - 14.2
Baseline Pain Level	
Mean \pm SD	5.9 \pm 1.6
Range	2.6 - 9.6
CD4 ⁺ Count (cells/mm ³)	
Mean \pm SD	434 \pm 280
Median	406
Range	12 - 1373
HIV-1 RNA (log ₁₀ copies/mL) ^a	
Mean \pm SD	3.32 \pm 0.91
Median	3.01
Range	2.60 - 5.82
Neurotoxic Antiretrovirals	
Not Taking	67 (82%)
Taking	15 (18%)
Concomitant Pain Medications	
Anticonvulsants	32 (39%)
Antidepressants	31 (38%)
Opioids	15 (18%)

^aFor HIV-1 RNA, values less than 400 copies/mL (i.e., below assay limit) are set to 400 (2.60 log₁₀) copies/mL to permit calculation of descriptive statistics.

Results

[0040] For Study 1, a total of 299 PHN subjects were enrolled. Of these, 222 were randomly assigned to receive the high-concentration (8% w/w) patch according to the duration of patch application (30, 60, or 90 minutes) and 77 were assigned to receive the low-concentration (0.04% w/w) patch. Overall 24 subjects (8%) terminated prematurely from the study, of which twenty subjects (9%) were in the high-concentration patch group and 4 subjects (5%) in the low-concentration group. Three subjects (1%) terminated due to adverse events in

the high-concentration patch group (2 subjects in the 90-minute and 1 subject in the 60-minute group). One subject in the low-concentration group died due to unrelated events of multi-organ failure, 108 days after study drug application. Overall, 275 subjects (91%) completed the double-blind study duration of 12 weeks. All randomized subjects were evaluated for safety and efficacy based on intent-to-treat (ITT) analysis.

[0041] For Study 2, a total of 155 PHN subjects were enrolled. Of these, 102 were randomly assigned to receive the high-concentration patch and 53 were assigned to receive the low-concentration patch. Overall 21 subjects (14%) terminated prematurely from the study of which, 11 subjects (11%) were in the active group and 10 subjects (19%) in the low-concentration group. None of the subjects terminated due to adverse events in the study. No deaths were reported in Study 2. Overall, 134 subjects (86%) completed the full study duration of 12 weeks. All 155 randomized subjects were evaluated for safety and efficacy based on intent-to-treat (ITT) analysis.

[0042] For Study 3, a total of 307 HIV-AN subjects were enrolled. Patients were randomized in a 3:3:3:1:1:1 ratio to receive either high-concentration ($640 \mu\text{g}/\text{cm}^2$ capsaicin) patches for durations of 30, 60 or 90 minutes or low-concentration ($3.2 \mu\text{g}/\text{cm}^2$ capsaicin) patches for 30, 60 or 90 minutes. Overall, 274 of 307 subjects (89%) completed the full study duration of 12 weeks. All 307 randomized subjects were evaluated for safety and efficacy based on intent-to-treat (ITT) analysis.

Efficacy in Study 1

[0043] The primary efficacy endpoint was the change from baseline in average pain intensity, as measured on an 11-point scale. The difference between the groups was computed by the difference between the high-concentration patch and the pooled low-concentration patch groups, with baseline pain as covariate. The effect in the low-concentration patch group was much larger than anticipated, particularly for those patients receiving 60-minute patch exposures. In this study, the low-concentration patches produced a significant and sustained decrease in pain.

Efficacy in Study 2

[0044] The mean percent change from baseline in the ‘average pain for the past 24 hours’ for Weeks 2-8 was -29.9% for subjects treated with the low-concentration patch. The results were consistent across other pain variables. For example, the mean percent change from baseline in the “worst pain for the past 24 hours” for Weeks 2-8 was -27.1% and the mean percent change from baseline in the “pain now” category for Weeks 2-8 was 31%.

Efficacy in Study 3

[0045] Those patients treated with the low-concentration capsaicin (this includes 30- 60 and 90-minute treatment groups) had an average pain reduction of 11% during weeks 2 to 12 (from baseline of 5.9 to 5.3). See Figure 2. 18% of subjects treated with the low-concentration capsaicin patch had $\geq 30\%$ pain decrease from baseline during weeks 2 to 12. Treatment-related adverse events consisted only of mild to moderate local reactions that resolved quickly.

[0046] Data from Study 3 were published as an abstract at the 13th Conference on Retroviruses and Opportunistic Infections (2006): “Controlled Study of High-Concentration Capsaicin Patch for Painful HIV-Associated Distal Sensory Polyneuropathy,” by D Simpson, S Brown, S Chang, J Jermano and C107 Study Group.

[0047] Pooled data from all patients in Studies 1, 2 and 3 receiving low-concentration capsaicin patch treatments is shown in Figure 2. For this graph, a weighted average of pain reduction per week is shown, along with a weighted standard error of the mean. The number of subjects represented by each data point varies between 185 to 208.

[0048] From the data generated by Studies 1, 2 and 3 it can be concluded that single treatments of low-concentration capsaicin patches provide long-term pain relief of neuropathic pain in a substantial percentage of patients. Pain relief has been observed in patients with both PHN and HIV-AN; this relief is statistically significant relative to baseline pain values and average pain relief values are only slightly less than induced by high-concentration capsaicin patches. There are no reports in scientific literature of sustained pain relief – lasting for at least 12 weeks – following treatments of neuropathic pain patients with placebos. Accordingly, it is not plausible that the sustained pain relief observed is due to merely psychological effects. Moreover, low-concentration patches have the added benefits of better tolerability during the

treatment procedure and not inducing any systemic capsaicin exposure. Thus overall, the therapeutic index – i.e., the ratio of benefit to adverse events or side effects – of the low-concentration patch is extremely high.

[0049] The utility of single topical low-concentration patch treatments is surprising, given current teachings regarding available capsaicin-based products. Although of approximately the same concentration range as over-the-counter products such as Zostrix[®] cream (0.075%) or Therapatch Warm with Capsaicin[®] (0.09%), the prescribing information for these and similar products provides no suggestion that single applications of either a cream or patch could provide 12 weeks of analgesic efficacy. In fact, the package insert for Zostrix[®] states that, “For optimum relief apply 3 to 4 times daily. Best results typically occur after 2 to 4 weeks of continuous use.” *In vitro* dermal drug delivery studies (conducted by the PRACS Institute, San Diego, CA, USA and Lohmann Therapie-Systeme, Andernach, Germany) have collectively indicated that the amount of capsaicin delivered into deeper skin (dermis) by Zostrix[®] is substantially lower than that delivered by the low-concentration patch. Accordingly, not all low-concentration products (either patches or creams) behave similarly and some low-concentration patches – particularly those which deliver capsaicin to deeper layers of the skin – may provide sustained pain reductions following single applications. The slow therapeutic response to Zostrix[®] applications is most likely a manifestation of its poor drug delivery efficiency.

[0050] The efficacy of topical applications of capsaicin patches is supported by an emerging understanding of the etiology of peripheral neuropathic pain. Capsaicin-sensitive nerve fibers in the skin are thought to be hyperactive in patients presenting with various peripheral neuropathic pain syndromes (Bley, K.R. Recent developments in transient receptor potential vanilloid receptor 1 agonist-based therapies. *Expert Opin Investig Drugs*. 2004. 13:1445-56.). Consequently, topical applications of capsaicin have long been recognized as a treatment option, due to the ability of capsaicin to inhibit nociceptor hyperactivity (Bley, K.R. Recent developments in transient receptor potential vanilloid receptor 1 agonist-based therapies. 2004. *Expert Opin Investig Drugs*.). This process of long-term nociceptor inhibition is known as “desensitization”, and is the goal of topical capsaicin therapy (Szallasi A, Blumberg PM. Vanilloid (capsaicin) receptors and mechanisms. *Pharmacol. Rev.* 1999. 51:159-212).

[0051] Due to the large number of patients treated, the data from Studies 1, 2 and 3 provide strong evidence for the efficacy of the low-concentration patch. Moreover, subject with

two etiologically distinct neuropathic pain syndromes were enrolled in these trials; this is suggestive of a broad-based efficacy against neuropathic pain.

[0052] The amount or dose of capsaicin which needs to be delivered into the skin for desensitization to occur is likely to vary between patients. The nervous system is very plastic, so following the multitude of injuries or lesions which can produce neuropathic pain, it is expected that the peripheral nervous system will respond in a variety of ways. One observed consequence is that nerve fibers which remain in the skin following neuropathic injury become hyperactive due to overexposure to neurotrophic factors and the subsequent expression of pro-excitatory proteins. TRPV1, the capsaicin receptor, is one of these pro-excitatory proteins. Consequently, in the cutaneous nerve fibers of some patients with peripheral neuropathic pain syndromes, TRPV1 over-expression may lead to dramatically increased sensitivity to capsaicin. Therefore capsaicin-induced desensitization could be initiated by much lower concentrations or doses of capsaicin than previously expected.

[0053] All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent, or patent application were specifically and individually indicated to be so incorporated by reference. Although the foregoing compositions and methods have been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of this description that certain changes and modifications may be made thereto without departing from the spirit and scope of the appended claims.

CLAIMS

What is claimed as new and desired to be protected by Letters Patent of the United States is:

1. A neuropathic pain-relieving patch comprising:

capsaicin or a capsaicin analog, wherein the concentration of the capsaicin or capsaicin analog is less than 1% by weight; and

a penetration enhancer, wherein the patch is capable of relieving neuropathic pain for a sustained period of time.
2. The neuropathic pain-relieving patch of claim 1 wherein the penetration enhancer is selected from the group consisting of ethers, esters, alcohols, fatty acids, terpenes, amines, and mixtures thereof.
3. The neuropathic pain-relieving patch of claim 1 wherein the penetration enhancer is selected from the group consisting of *l*-menathone, dimethyl isosorbide, caprylic alcohol, lauryl alcohol, oleyl alcohol, ethylene glycol, diethylene glycol monoethyl ether, triethylene glycol, butylene glycol, valeric acid, pelargonic acid, caproic acid, caprylic acid, lauric acid, oleic acid, isovaleric acid, isopropyl butyrate, isopropyl hexanoate, butyl acetate, methyl acetate, methyl valerate, ethyl oleate, poloxamer, *d*-piperitone, methylnonenoic acid, methylnonenoic alcohol, and *d*-pulegone, and mixtures thereof.
4. The neuropathic pain-relieving patch of claim 3 wherein the penetration enhancer is diethylene glycol monoethyl ether.
5. The neuropathic pain-relieving patch of claim 1 further comprising a self-adhesive matrix.
6. The neuropathic pain-relieving patch of claim 5 wherein the self-adhesive matrix comprises an amine-resistant polysiloxane.

7. The neuropathic pain-relieving patch of claim 6 wherein the amine resistant polysiloxane comprises a mixture of medium and high tack polysiloxane.

8. The neuropathic pain-relieving patch of claim 6 further comprising about 0.5% to about 5% by weight of a silicone oil.

9. The neuropathic pain-relieving patch of claim 1 further comprising a viscosity increasing agent.

10. The neuropathic pain-relieving patch of claim 9 wherein the viscosity increasing agent is ethylcellulose, hydropropylcellulose, or mixtures thereof.

11. The neuropathic pain-relieving patch of claim 1 further comprising a backing layer.

12. The neuropathic pain-relieving patch of claim 11 wherein the backing layer comprises a polyester film.

13. The neuropathic pain-relieving patch of claim 11 wherein the backing layer is about 10 to about 20 μm thick.

14. A neuropathic pain-relieving patch comprising:

0.04% by weight or less of capsaicin or a capsaicin analog;

10-20% by weight of diethylene glycol monoethyl ether;

0-2% by weight of ethylcellulose;

0-5% by weight of silicone oil; and

58-85% by weight of a self-adhesive polysiloxane.

15. The neuropathic pain-relieving patch of claim 14 further comprising a backing layer.

16. The neuropathic pain-relieving patch of claim 15 wherein the backing layer comprises a polyester film

17. The neuropathic pain-relieving patch of claim 14 wherein the backing layer is about 10 to about 20 μm thick.

18. A neuropathic pain-relieving patch comprising:

capsaicin, or a capsaicin analog, wherein the concentration of the capsaicin or capsaicin analog is less than 1%; and

a penetration enhancer, wherein delivery of capsaicin from the patch continues for at least an hour, and wherein a single use of the patch provides a therapeutic benefit for at least one month.

19. The neuropathic pain-relieving patch of claim 18 wherein the penetration enhancer is selected from the group consisting of ethers, esters, alcohols, fatty acids, terpenes, amines, and mixtures thereof.

20. The neuropathic pain-relieving patch of claim 18 wherein the penetration enhancer is selected from the group consisting of *l*-menathone, dimethyl isosorbide, caprylic alcohol, lauryl alcohol, oleyl alcohol, ethylene glycol, diethylene glycol monoethyl ether, triethylene glycol, butylene glycol, valeric acid, pelargonic acid, caproic acid, caprylic acid, lauric acid, oleic acid, isovaleric acid, isopropyl butyrate, isopropyl hexanoate, butyl acetate, methyl acetate, methyl valerate, ethyl oleate, poloxamer, *d*-piperitone, methylnonenoic acid, methylnonenoic alcohol, and *d*-pulegone, and mixtures thereof.

21. The neuropathic pain-relieving patch of claim 20 wherein the penetration enhancer is diethylene glycol monoethyl ether.

22. The neuropathic pain-relieving patch of claim 18 further comprising a self-adhesive matrix.

23. The neuropathic pain-relieving patch of claim 22 wherein the self-adhesive matrix comprises an amine-resistant polysiloxane.

24. The neuropathic pain-relieving patch of claim 23 wherein the amine resistant polysiloxane comprises a mixture of medium and high tack polysiloxane.

25. The neuropathic pain-relieving patch of claim 23 further comprising about 0.5% to about 5% by weight of a silicone oil.

26. The neuropathic pain-relieving patch of claim 18 further comprising a viscosity increasing agent.

27. The neuropathic pain-relieving patch of claim 26 wherein the viscosity increasing agent is ethylcellulose, hydropropylcellulose, or mixtures thereof.

28. The neuropathic pain-relieving patch of claim 18 further comprising a backing layer.

29. The neuropathic pain-relieving patch of claim 28 wherein the backing layer comprises a polyester film.

30. The neuropathic pain-relieving patch of claim 28 wherein the backing layer is about 10 to about 20 μm thick.

31. The neuropathic pain-relieving patch of claim 18 wherein a single use of the patch provides a therapeutic benefit for at least two months.

32. The neuropathic pain-relieving patch of claim 18 wherein a single use of the patch provides a therapeutic benefit for at least three months.

33. A method for treating neuropathic pain comprising the step of dermally delivering a single administration of capsaicin or a capsaicin analog, wherein the concentration of the capsaicin or capsaicin analog is less than 1%.

34. The method of claim 33 wherein the dermal delivery of the capsaicin or capsaicin analog provides a therapeutic benefit for at least one month.

35. The method of claim 34 wherein the dermal delivery of the capsaicin or capsaicin analog provides a therapeutic benefit for at least two months.

36. The method of claim 34 wherein the dermal delivery of the capsaicin or capsaicin analog provides a therapeutic benefit for at least three months.

37. A method for treating neuropathic pain by applying the patch of claim 1 to an area of skin.

38. A method for treating neuropathic pain by applying the patch of claim 14 to an area of skin.

39. A method for treating neuropathic pain by applying the patch of claim 18 to an area of skin.

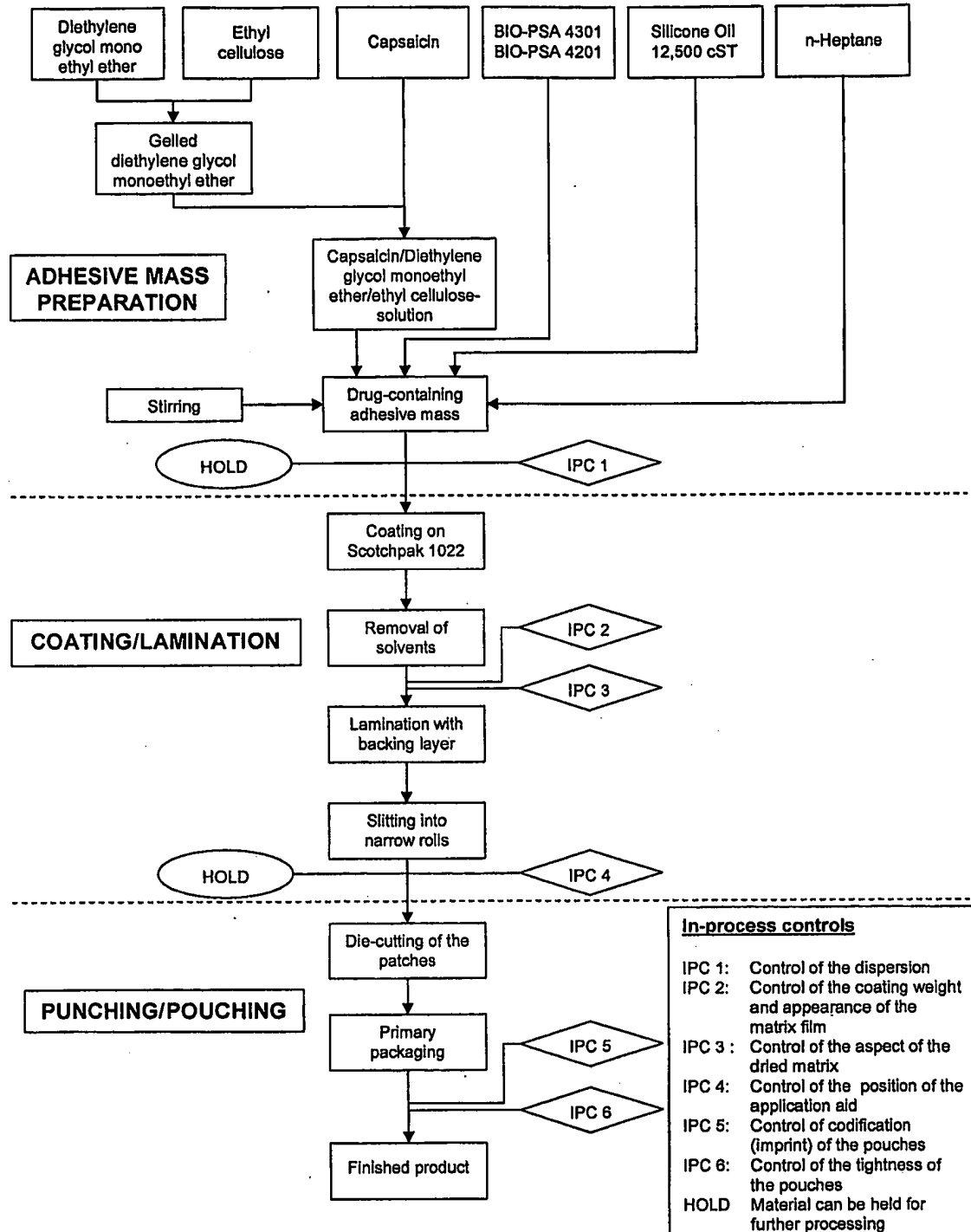
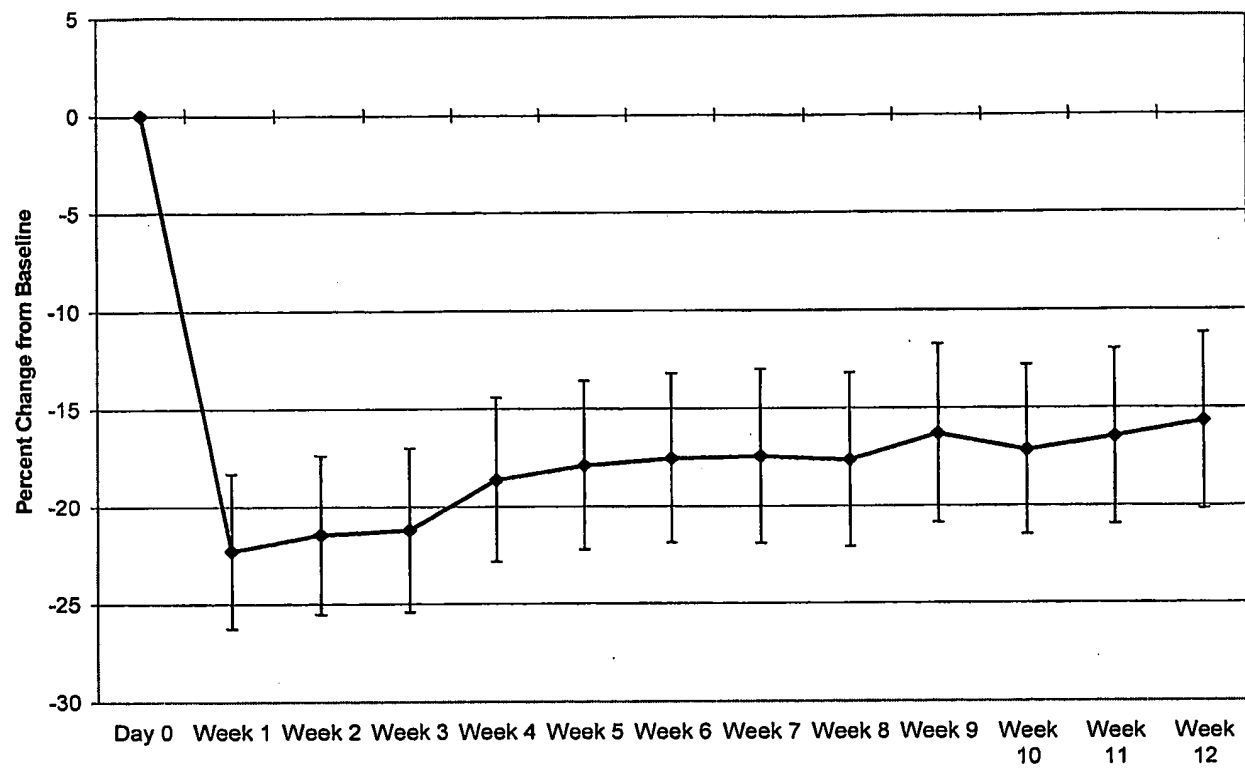


FIG. 1

FIG. 2



INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/012271

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/70 A61K31/165 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, FSTA, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 665 378 A (DAVIS ET AL) 9 September 1997 (1997-09-09) column 3, line 17 - line 27 column 6; example 1 column 5, line 2 - line 33 claims 1,5	1,2,5,9, 11,13, 18,19, 22,26, 28, 30-37,39
X	WO 98/53825 A (ALGOS PHARMACEUTICAL CORPORATION; CARUSO, FRANK, S) 3 December 1998 (1998-12-03) page 7, line 23 - page 8, line 25 claims 1-9	1,5,11, 13,18, 22,28, 30-37,39



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

6 July 2006

Date of mailing of the international search report

25/07/2006

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/012271

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 869 533 A (HOLT ET AL) 9 February 1999 (1999-02-09)	1-3, 5, 9, 11, 13, 18-20, 22, 26, 28, 30-37, 39
Y	column 7; example 1 claims 1-8 column 3, line 13 - line 41 column 1, line 10 - line 45 column 6, line 35 - line 55 -----	4, 6-8, 10, 12, 14-17, 21, 23-25, 27, 29, 38
Y	WO 2004/089361 A (LTS LOHMANN THERAPIE-SYSTEME AG; MUELLER, WALTER) 21 October 2004 (2004-10-21) claims 1, 2, 6-8, 11-15, 17, 18 -----	4, 6-8, 10, 12, 14-17, 21, 23-25, 27, 29, 38
A	US 2001/002406 A1 (ROBBINS WENDYE R) 31 May 2001 (2001-05-31) claims 1-11 page 1, paragraphs 3, 4 page 2, paragraph 15 -----	1-39
P, X	EP 1 568 365 A (HISAMITSU PHARMACEUTICAL CO. INC) 31 August 2005 (2005-08-31) page 8; example 1 claims 1-7 -----	1, 2, 5, 6, 9, 11-13, 18, 19, 22, 26, 28-37, 39

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/012271

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 33 - 39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/012271

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